

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
15 April 2004 (15.04.2004)

PCT

(10) International Publication Number  
**WO 2004/031204 A3**

(51) International Patent Classification<sup>7</sup>: **C07J 21/00**,  
75/00

(21) International Application Number:  
PCT/PL2003/000099

(22) International Filing Date: 1 October 2003 (01.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
P.356465 4 October 2002 (04.10.2002) PL

(71) Applicant (for all designated States except US): **PRZED-  
SIĘBIORSTWO FARMACEUTYCZNE ANPHARM**  
S.A. [PL/PL]; ul. Annopol 6B, PL-03-236 Warszawa (PL).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **MARTYNOW**,  
Jacek [PL/PL]; ul. Renesansowa 25 m. 5, PL-01  
905 Warszawa (PL). **KUTNER, Andrzej** [PL/PL];  
ul. Surowieckiego 8 m.12, PL-02-785 Warszawa (PL).  
**SZELEJEWSKI, Wiesław** [PL/PL]; ul. Sw. Patryka 2

m.15, PL-03-980 Warszawa (PL). **WOJCIECHOWSKA**,  
Wanda [PL/PL]; ul. Kobuza 17, PL-02-841 Warszaw  
(PL). **FITAK, Hanna** [PL/PL]; Al. Reymonta 23 m.261,  
PL-01-840 Warszawa (PL).

(74) Agent: **KOSEK, Maria**; Przedsiębiorstwo farmaceuty-  
czne Anpharm S.A., ul. Annopol 6B, PL-03-236 Warszawa  
(PL).

(81) Designated States (national): AL, AM, AT, AU, AZ, BA,  
BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB,  
GE, HR, HU, IL, IN, IS, JP, KG, KR, KZ, LC, LT, LU, LV,  
MD, MK, MX, NO, NZ, PT, RO, RU, SE, SG, SK, SY, TJ,  
TM, TR, UA, US, UZ, YU, ZA.

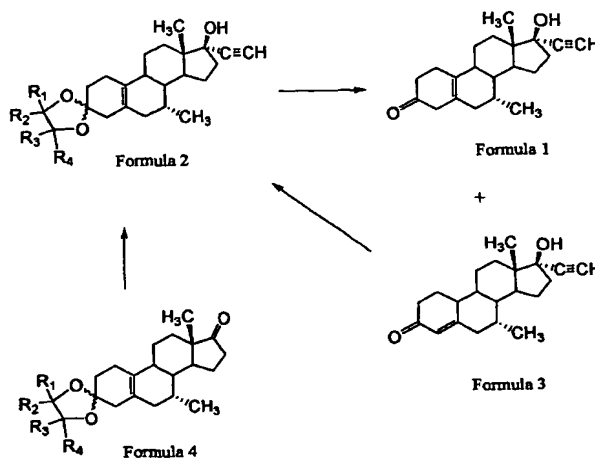
(84) Designated States (regional): Eurasian patent (AM, AZ,  
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,  
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU,  
IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

#### Declaration under Rule 4.17:

— as to applicant's entitlement to apply for and be granted  
a patent (Rule 4.17(ii)) for the following designations AL,  
AM, AT, AU, AZ, BA, BG, BR, BY, CA, CH, CN, CZ, DE,  
DK, EE, ES, FI, GB, GE, HR, HU, IL, IN, IS, JP, KG, KR,

[Continued on next page]

(54) Title: PROCESS AND INTERMEDIATES TO PREPARE 17.BETA.-HYDROXY-7.ALFA.-METHYL-19-NOR-17.ALFA.-  
PREGN-5(10)-EN-20-YN-3-ONE



(57) Abstract: The present invention is a process for the preparation of 17 $\beta$ -hydroxy-7 $\alpha$ -methyl-19-nor-17 $\alpha$ -pregn-5(10)-en-20-yn-3-one (17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-7 $\alpha$ -methyl-5(10)-estren-3-one, tibolone) of formula 1, which comprises hydrolysis of 17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-7 $\alpha$ -methyl-5(10)-estren-3-one, where groups R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> and R<sub>4</sub> are hydrogen atoms or alkyl groups, or R<sub>1</sub> and R<sub>3</sub>, taken together with the carbon atoms within the dioxolane ring to which they are attached, form an alicyclic ring fused to the dioxolane ring, with R<sub>2</sub> and R<sub>4</sub> being hydrogen atoms, or R<sub>1</sub> and R<sub>3</sub> together with the carbon atoms to which they are attached form an aromatic ring fused to the dioxolane ring, where R<sub>2</sub> and R<sub>4</sub>, taken together, form a chemical bond within said aromatic ring. In addition, the present invention includes an intermediate, compound of formula 2 and two processes to prepare 17 $\alpha$ -ethynyl-17(3-hydroxy-7 $\alpha$ -methyl-5(10)-estren-3-one 3,3-cyclic ketals of formula 2: (a) by contacting 17 $\alpha$ -ethynyl-17 $\beta$ -hydroxy-7 $\alpha$ -methyl-4-estren-3-one with vicinal diols in the presence of a protic acid, and (b) by contacting 7 $\alpha$ -methyl-5(10)-estren-17-one 3,3-cyclic ketals of formula 4, where R<sub>1</sub>-R<sub>4</sub> are defined as above, with metal acetylides, in inert solvents.



KZ, LC, LT, LU, LV, MD, MK, MX, NO, NZ, PT, RO, RU, SE, SG, SK, SY, TJ, TM, TR, UA, UZ, YU, ZA, Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR)

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

**Published:**

— with international search report

**(88) Date of publication of the international search report:**

1 July 2004

## INTERNATIONAL SEARCH REPORT

Inter. Application No

PC 03/00099

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C07J21/00 C07J75/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07J

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data, BIOSIS, EMBASE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DINUNNO, CECIL M. ET AL: "7.alpha.-Methylnorethindrone enanthate 10.beta.-hydroperoxide: isolation and characterization" STEROIDS (1983), 42(4), 401-8 , XP009027390 page 404, line 10-21 compound III page 406, paragraphs 2,3 --- -/--	17-20

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

11 March 2004

Date of mailing of the international search report

17/03/2004

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Guspanova, J

# INTERNATIONAL SEARCH REPORT

International Application No  
PC 03/00099

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	HOYTE, ROBERT M. ET AL: "7.alpha.-Methyl-17.alpha.-(E-2' '125I!iodo vinyl)-19-nortestosterone: a new radioligand for the detection of androgen receptor" STEROIDS, vol. 58, no. 1, 1993, pages 13-23, XP009027391	17-20
Y	page 15, column 1, paragraph 1; figure 1	1-8, 12-16, 21-23
X	US 4 308 265 A (BLYE RICHARD ET AL) 29 December 1981 (1981-12-29) cited in the application	17,18
Y	column 2, line 65 -column 3, line 13; example 3	1-8, 12-16, 21-23
Y	VAN VLIET N P ET AL: "An alternative synthesis of 17.beta.-hydroxy-7.alpha.-methyl-19-nor-17.alpha.-pregn-5(10)-en-20-yn-3-one (Org OD 14)" RECUEIL DES TRAVAUX CHIMIQUES DES PAYS-BAS, ELSEVIER SCIENCE PUBLISHERS. AMSTERDAM, NL, vol. 105, no. 4, April 1986 (1986-04), pages 111-115, XP002099865 ISSN: 0165-0513 cited in the application Scheme 2, compounds 4, 13 and 21 page 115, column 1, paragraph 3 -page 115, column 2, paragraph 1	1-8, 12-16, 21-23
Y	WO 00 23460 A (KIRCHHOLTES PETER HUUB GERARD ;SAS GERARD ARNOUD JOZEF MARIA (NL);) 27 April 2000 (2000-04-27) cited in the application page 2, paragraph 6 -page 3, paragraph 2; examples 1-3	1-8, 12-16, 21-23
Y	US 3 534 139 A (BUCOURT ROBERT ET AL) 13 October 1970 (1970-10-13)  example 1	1-8, 12-16, 21-23
Y	US 4 945 064 A (HOFMEISTER HELMUT ET AL) 31 July 1990 (1990-07-31) cited in the application column 3, line 33-38; example 4	14-16

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 4308265	A	29-12-1981	US 4252800 A	24-02-1981
WO 0023460	A	27-04-2000	AT 239032 T	15-05-2003
			AU 763232 B2	17-07-2003
			AU 6202999 A	08-05-2000
			BR 9914441 A	26-06-2001
			CA 2344686 A1	27-04-2000
			CN 1322210 T	14-11-2001
			CZ 20010976 A3	15-08-2001
			DE 69907495 D1	05-06-2003
			DK 1121375 T3	04-08-2003
			WO 0023460 A1	27-04-2000
			EP 1275379 A2	15-01-2003
			EP 1121375 A1	08-08-2001
			ES 2197677 T3	01-01-2004
			HK 1039620 A1	22-08-2003
			HU 0104206 A2	29-04-2002
			ID 28463 A	24-05-2001
			JP 2002527525 T	27-08-2002
			NO 20011664 A	03-04-2001
			NZ 510501 A	31-10-2003
			PL 347264 A1	25-03-2002
			PT 1121375 T	31-07-2003
			SK 4932001 A3	03-12-2001
			TR 200101083 T2	21-08-2001
			ZA 200101952 A	10-06-2002
US 3534139	A	13-10-1970	FR 1519509 A	05-04-1968
			AT 263231 B	10-07-1968
			BE 677698 A	12-09-1966
			CH 457423 A	15-06-1968
			DE 1298993 B	10-07-1969
			DK 116281 B	29-12-1969
			FR 4751 M	
			GB 1085282 A	27-09-1967
			GB 1085283 A	27-09-1967
			IL 25326 A	31-12-1969
			NL 128815 C	
			NL 6603268 A	19-09-1966
			US 3622896 A	23-11-1971
US 4945064	A	31-07-1990	DE 3337179 A1	23-05-1985
			AT 72247 T	15-02-1992
			AU 3406684 A	11-09-1986
			CA 1300601 C	12-05-1992
			DE 3485490 D1	12-03-1992
			DK 484584 A	11-04-1985
			EP 0137434 A2	17-04-1985
			ES 8506326 A1	01-11-1985
			GR 80583 A1	04-02-1985
			IE 58642 B1	20-10-1993
			JP 1911094 C	09-03-1995
			JP 6035476 B	11-05-1994
			JP 60155193 A	15-08-1985
			NZ 209811 A	29-02-1988